

CLAIMS:

1. A stable liposome composition for delivering a pharmaceutical agent, the composition comprising:

- 5 (a) a suitable aqueous medium;
- (a) liposomes formed from a suitable phospholipid;
- (b) at least one pharmaceutical agent being at least partially encapsulated in the liposomes, and being selected from:
- 10 (i) a lipophilic amine and a pharmaceutically acceptable acid, wherein the pharmaceutically acceptable acid is selected from an organic or inorganic acid, and
- (ii) a pharmaceutically acceptable organic acid salt of a lipophilic amine, and optionally a pharmaceutically acceptable acid comprising a pharmaceutically acceptable organic acid;
- 15 wherein the quantity of the pharmaceutically acceptable acid present in the composition is such that the pH of the liposome composition is less than or approximately equal to the pK_a of the amino group of the pharmaceutically active lipophilic amine.
2. A composition according to claim 1, wherein the pH of the liposome composition
- 20 is about equal to the pK_a of the amino group of the lipophilic amine, and about 50% of the lipophilic amine is protonated in the composition.
3. A composition according to claim 1, wherein the pH of the liposome composition is less than the pK_a of the amino group of the lipophilic amine, and a major portion of the lipophilic amine is protonated in the composition.
- 25 4. A composition according to claim 1, wherein the composition has a pH of about 1 to about 2 pH units below the pK_a of the amino group of the lipophilic amine.

5. A composition according to claim 1, wherein the pH of the liposome composition is between about 4 and the pK_a of the amino group of the lipophilic amine.
6. A composition according to claim 1 wherein the composition has a pH of between about 4 and about 8.
- 5 7. A composition according to claim 6, wherein the composition has a pH of between about 4 to about 7.
8. A composition according to claim 6, wherein the composition has a pH of between about 4.5 and about 6.5.
9. A composition according to claim 6, wherein the composition has a pH of
10 between about 5 and about 6.
10. A composition according to claim 1, further comprising cholesterol.
11. A composition according to claim 1, further comprising ethanol.
12. A composition according to claim 11, wherein the ethanol is present at between about 2.5 % and about 10% of the total volume of the liposome composition.
- 15 13. A composition according to claim 1, wherein the phospholipid has a net neutral charge at about physiological pH.
14. A composition of claim 13, wherein the phospholipid comprises phosphatidylcholine.
15. A composition according to claim 1, wherein the aqueous medium is water.
- 20 16. A composition according to claim 1, wherein the pharmaceutical agent is also free in the aqueous medium.
17. A composition according to claim 16, wherein the percent of liposome encapsulated pharmaceutical agent comprises about 50% to about 90% of the total amount of pharmaceutical agent present in the liposome composition.

18. A composition according to claim 17, wherein the percent of liposome encapsulated pharmaceutical agent comprises about 60% to about 80% of the total amount of pharmaceutical agent present in the liposome composition.
19. A composition according to claim 18, wherein the percent of liposome encapsulated pharmaceutical agent comprises about 50% to about 75% of the total amount of pharmaceutical agent present in the liposome composition.
20. A composition according to claim 1, wherein the pharmaceutically acceptable acid of step (b)(i) comprises an organic acid.
21. A composition according to claim 1, wherein the pharmaceutically acceptable acid of step (b)(i) comprises an inorganic acid.
22. A composition according to claim 1, wherein the liposome particles of the liposome composition have a mass median diameter ($d(0.5)$) of less than about 10 microns.
23. A composition according to claim 22, wherein the liposome particles of the liposome composition have a mass median diameter ($d(0.5)$) of less than about 6 microns.
24. A composition according to claim 22, wherein the liposome particles of the liposome composition have a mass median diameter ($d(0.5)$) of less than 4 microns.
25. A composition according to claim 22, wherein the liposome particles of the liposome composition have a mass median diameter ($d(0.5)$) of less than about 2 microns.
26. A composition according to claim 1, wherein the lipophilic amine comprises a lipophilic amine that has a log P value of greater than about 1.0 at physiological pH.

27. A composition according to claim 26, wherein the lipophilic amine has a log P value of between about 2 and about 5 at physiological pH.
28. A composition of claim 1, wherein the ratio of pharmaceutical agent to phospholipid is about between 1:100 and about 1:10 mol/mol.
- 5 29. A composition of claim 1, wherein the amount of phospholipid present is about 1.5 mM or more in the composition.
30. A composition according to claim 1, wherein upon centrifugation at a g-force of about between about 1000 and about 5000, a temperature of about 4°C, and a time period of about 2 hours, the ratio of the particle size distribution of the liposomes
10 of the liposome composition after centrifugation relative to that prior to centrifugation is equal to or greater than about 0.6.
31. A composition according to any of claims 1-30, wherein said liposome composition is autoclaved and said composition is physically and chemically stable to autoclaving.
- 15 32. A composition according to any of claims 1-30, wherein the liposome composition is autoclaved and said composition is physically and chemically stable to autoclaving at a temperature of about 121°C for a minimum of about 15 minutes.
33. A composition according to claim 31, wherein the liposome compositions are
20 physically and chemically stable for at least about one year at a temperature above the freezing point of the liposome compositions.
34. A composition according to claim 31, wherein the liposome compositions are physically and chemically stable for at least 18 months at a temperature above the freezing point of the liposome compositions.
- 25 35. A composition according to claim 31, wherein the liposome compositions are physically and chemically stable for at least 24 months at a temperature above the freezing point of the liposome compositions.

36. A composition according to claim 31, wherein the percent encapsulation of drug in the liposome composition is substantially stable over a period of at least 20 months under an inert atmosphere.
- 5 37. A composition according to claim 31, wherein the amount of phospholipid does not chemically degrade by more than about 10% (weight/weight) over a period of at least 20 months.
38. A composition according to claim 31, wherein the amount of phospholipid does not chemically degrade by more than about 5% (weight/weight) over a period of at least 20 months.
- 10 39. A composition according to claim 31, wherein the lipophilic amine does not chemically degrade by more than about 5% (weight/weight) over a period of at least 20 months.
40. A composition according to claim 31, wherein the lipophilic amine does not chemically degrade by more than about 2% (weight/weight) over a period of at least 20 months.
- 15 41. A sterile and stable liposome composition for delivering a pharmaceutical agent, the composition comprising:
- (a) a suitable aqueous medium;
 - (a) liposomes formed from a suitable phospholipid;
 - 20 (b) at least one pharmaceutical agent being at least partially encapsulated in the liposomes, and being selected from:
 - (i) a lipophilic amine and a pharmaceutically acceptable acid, wherein the pharmaceutically acceptable acid is selected from an organic or inorganic acid, and

- (ii) a pharmaceutically acceptable organic acid salt of a lipophilic amine, and optionally a pharmaceutically acceptable organic acid, and optionally a pharmaceutically acceptable acid comprising a pharmaceutically acceptable organic acid;

5 wherein the composition is autoclaved, and wherein quantity of the pharmaceutically acceptable acid present in the composition is such that the pH of the liposome composition is less than or approximately equal to the pK_a of the amino group of the pharmaceutically active lipophilic amine.

10 42. A sterile and stable composition according to claim 41, wherein the pH of the liposome composition is about equal to the pK_a of the amino group of the lipophilic amine, and about 50% of the lipophilic amine is protonated in the composition.

15 43. A sterile and stable composition according to claim 41, wherein the pH of the liposome composition is less than the pK_a of the amino group of the lipophilic amine, and a major portion of the lipophilic amine is protonated in the composition.

20 44. A sterile and stable composition according to claim 41, wherein the composition has a pH of about 1 to about 2 pH units below the pK_a of the amino group of the lipophilic amine.

45. A sterile and stable composition according to claim 41, wherein the pH of the liposome composition is between about 4 and the pK_a of the amino group of the lipophilic amine.

25 46. A sterile and stable composition according to claim 41, wherein the composition has a pH of between about 4 and about 8.

47. A sterile and stable composition according to claim 46, wherein the composition has a pH of between about 4 to about 7.

48. A sterile and stable composition according to claim 47, wherein the composition has a pH of between about 4.5 and about 6.5.
49. A sterile and stable composition according to claim 48, wherein the composition has a pH of between about 5 and about 6.
- 5 50. A sterile and stable composition according to claim 41, further comprising cholesterol.
51. A sterile and stable composition according to claim 41, further comprising ethanol.
- 10 52. A sterile and stable composition according to claim 51, wherein the ethanol is present at between about 2.5 % and about 10% of the total volume of the liposome composition.
53. A sterile and stable composition according to claim 41, wherein the phospholipid has a net neutral charge at about physiological pH.
- 15 54. A sterile and stable composition according to claim 53, wherein the phospholipid comprises phosphatidylcholine.
55. A sterile and stable composition according to claim 41, wherein the aqueous medium is water.
56. A sterile and stable composition according to claim 41, wherein the pharmaceutical agent is also free in the aqueous medium.
- 20 57. A sterile and stable composition according to claim 56, wherein the percent of liposome encapsulated pharmaceutical agent comprises about 50% to about 90% of the total amount of pharmaceutical agent present in the liposome compositions.
- 25 58. A sterile and stable composition according to claim 57, wherein the percent of liposome encapsulated pharmaceutical agent comprises about 60% to about 80% of the total amount of pharmaceutical agent present in the liposome compositions.

59. A sterile and stable composition according to claim 58, wherein the percent of liposome encapsulated pharmaceutical agent comprises about 50% to about 75% of the total amount of pharmaceutical agent present in the liposome composition.
60. A sterile and stable composition according to claim 41, wherein the pharmaceutically acceptable acid of step b(i) comprises an organic acid.
61. A sterile and stable composition according to claim 41, wherein the pharmaceutically acceptable acid of step b(i) comprises an inorganic acid.
62. A sterile and stable composition according to claim 41, wherein the liposome particles of the liposome composition have a mass median diameter ($d(0.5)$) of less than about 10 microns.
63. A sterile and stable composition according to claim 62, wherein the liposomes have a mass median diameter ($d(0.5)$) of less than about 6 microns.
64. A sterile and stable composition according to claim 63, wherein the liposomes have a mass median diameter ($d(0.5)$) of less than 4 microns.
65. A sterile and stable composition according to claim 64, wherein the liposomes have a mass median diameter ($d(0.5)$) of less than about 2 microns.
66. A sterile and stable composition according to claim 41, wherein the liposome compositions are physically and chemically stable and sterile for at least about one year at a temperature above the freezing point of the liposome compositions.
67. A sterile and stable composition according to claim 66, wherein the liposome compositions are physically and chemically stable and sterile for at least 18 months at a temperature above the freezing point of the liposome compositions.
68. A sterile and stable composition according to claim 67, wherein the liposome compositions are physically and chemically stable and sterile for at least 24 months at a temperature above the freezing point of the liposome compositions.

69. A sterile and stable composition according to claim 41, wherein the lipophilic amine comprises a lipophilic amine that has a log P value of greater than about 1.0 at physiological pH.
70. A sterile and stable composition according to claim 41, wherein the lipophilic amine has a log P value of between about 2 and about 5 at physiological pH.
71. A sterile and stable composition according to claim 41, wherein the ratio of pharmaceutical agent to phospholipid is between about 1:100 and 1:10 mol/mol.
72. A sterile and stable composition according to claim 41, wherein the amount of phospholipids present is about 1.5 mM or more in the composition.
73. A sterile and stable composition according to claim 41, wherein the percent encapsulation of drug in the liposome composition is substantially stable over a period of at least 20 months.
74. A sterile and stable composition according to claim 41, wherein the compositions are substantially chemically stable over a period of at least 20 months.
75. A sterile and stable composition according to claim 41, wherein the amount of phospholipid does not decrease due to chemical degradation by more than about 10% (weight/weight) over a period of at least 20 months.
76. A sterile and stable composition according to claim 41, wherein the amount of phospholipid does not decrease due to chemical degradation by more than about 5% (weight/weight) over a period of at least 20 months.
77. A sterile and stable composition according to claim 41, wherein the lipophilic amine does not chemically degrade by more than about 5% (weight/weight) over a period of at least 20 months.
78. A sterile and stable composition according to claim 41, wherein the lipophilic amine does not chemically degrade by more than about 2% (weight/weight) over a period of at least 20 months.

79. A method for producing a stable liposome composition for delivering a pharmaceutical agent, the method comprising the steps of:
- (a) providing a suitable aqueous medium;
 - (b) providing a suitable phospholipid;
 - 5 (c) providing at least one pharmaceutical agent being capable of being at least partially encapsulated in the liposomes, and being selected from:
 - (i) a lipophilic amine and a pharmaceutically acceptable acid, wherein the pharmaceutically acceptable acid is selected from an organic or inorganic acid, and
 - 10 (ii) a pharmaceutically acceptable organic acid salt of a lipophilic amine, and optionally a pharmaceutically acceptable acid comprising a pharmaceutically acceptable organic acid;
- wherein the quantity of the pharmaceutically acceptable acid present in the composition is such that the pH of the liposome composition is less than
- 15 or approximately equal to the pK_a of the amino group of the pharmaceutically active lipophilic amine;
- (d) combining the aqueous medium, phospholipid and pharmaceutical agent to form the liposome composition; and
 - (e) optionally autoclaving said composition.
- 20 80. The method according to claim 79, wherein the liposome composition is autoclaved, and wherein the composition is a sterile composition.
81. The method according to claim 79 or 80, wherein the pH of the liposome composition is about equal to the pK_a of the amino group of the lipophilic amine, and about 50% of the lipophilic amine is protonated in the composition.

82. The method according to claim 79 or 80, wherein the pH of the liposome composition is less than the pK_a of the amino group of the lipophilic amine, and a major portion of the lipophilic amine is protonated in the composition.
- 5 83. The method according to claim 79 or 80, wherein the composition has a pH of about 1 to about 2 pH units below the pK_a of the amino group of the lipophilic amine.
84. The method according to claim 79 or 80, wherein the pH of the liposome composition is between about 4 and the pK_a of the amino group of the lipophilic amine.
- 10 85. The method according to claim 79 or 80, wherein the composition has a pH of between about 4 and about 8.
86. The method according to claim 79 or 80, wherein the composition has a pH of between about 4 to about 7.
- 15 87. The method according to claim 79 or 80, wherein the composition has a pH of between about 4.5 and about 6.5.
88. The method according to claim 79 or 80, wherein the composition has a pH of between about 5 and about 6.
- 20 89. The method according to claim 79 or 80, wherein at least one of cholesterol and ethanol is further provided, and step (d) comprises the step of combining the aqueous medium, phospholipids, pharmaceutical agent, and the at least one of cholesterol and ethanol to form the liposome compositions.
90. The method according to claim 89, wherein ethanol is present at between about 2.5 % and about 10% of the total volume of the liposome composition.
- 25 91. The method according to claim 79 or 80, wherein the phospholipid has a net neutral charge at about physiological pH.

92. The method according to claim 79 or 80, wherein the phospholipid comprises phosphatidylcholine.
93. The method according to claim 79 or 80, wherein the aqueous medium is water.
94. The method according to claim 79 or 80, wherein the pharmaceutical agent is
5 also free in the aqueous medium.
95. The method according to claim 79 or 80, wherein the percent of liposome encapsulated pharmaceutical agent comprises about 50% to about 90% of the total amount of pharmaceutical agent present in the liposome composition.
96. The method according to claim 79 or 80, wherein the percent of liposome
10 encapsulated pharmaceutical agent comprises about 60% to about 80% of the total amount of pharmaceutical agent present in the liposome composition.
97. The method according to claim 79 or 80, wherein the percent of liposome encapsulated pharmaceutical agent comprises about 50% to about 75% of the total amount of pharmaceutical agent present in the liposome composition.
- 15 98. The method according to claim 79 or 80, wherein the pharmaceutically acceptable acid of step c(i) comprises an organic acid.
99. The method according to claim 79 or 80, wherein the pharmaceutically acceptable acid of step c(i) comprises an inorganic acid.
100. The method according to claim 79 or 80, wherein the liposome particles of the
20 liposome composition have a mass median diameter ($d(0.5)$) of less than about 10 microns.
101. The method according to claim 100, wherein the liposome particles of the liposome composition have a mass median diameter ($d(0.5)$) of less than about 6 microns.

102. The method according to claim 100, wherein the liposomes have a mass median diameter (d(0.5)) of less than 4 microns.
103. The method according to claim 100, wherein the liposomes have a mass median diameter (d(0.5)) of less than about 2 microns.
- 5 104. The method according to claim 79 or 80, wherein the liposome compositions are physically and chemically stable and sterile for at least about one year at a temperature above the freezing point of the liposome compositions.
105. The method according to claim 79 or 80, wherein the liposome compositions are physically and chemically stable and sterile for at least 18 months at a
10 temperature above the freezing point of the liposome compositions.
106. The method according to claim 79 or 80, wherein the liposome compositions are physically and chemically stable and sterile for at least 24 months at a temperature above the freezing point of the liposome compositions.
107. The method according to claim 79 or 80, wherein the lipophilic amine comprises
15 a lipophilic amine that has a log P value of greater than about 1.0 at physiological pH.
108. The method according to claim 79 or 80, wherein the lipophilic amine has a log P value of between about 2 and about 5 at physiological pH.
109. The method according to claim 79 or 80, wherein the ratio of pharmaceutical
20 agent to phospholipid is about between 1:100 and 1:10 mol/mol.
110. The method according to claim 80, wherein the amount of phospholipids present is about 1.5 mM or more in the composition.
111. The method according to claim 80, wherein the percent encapsulation of drug in the liposome composition is substantially stable over a period of at least 20
25 months.

112. The method according to claim 80, wherein the compositions are substantially chemically stable over a period of at least 20 months.
113. The method according to claim 80, wherein the amount of phospholipid does not decrease due to chemical hydrolysis or oxidation by more than about 10% (weight/weight) over a period of at least 20 months.
114. The method according to claim 80, wherein the amount of phospholipid does not decrease due to chemical hydrolysis or oxidation by more than about 5% (weight/weight) over a period of at least 20 months.
115. The method according to claim 80, wherein the lipophilic amine does not chemically degrade by more than about 5% (weight/weight) over a period of at least 20 months.
116. The method according to claim 80, wherein the lipophilic amine does not chemically degrade by more than about 2% (weight/weight) over a period of at least 20 months.
117. A sterile and stable liposome composition according to claim 41, exhibiting one or more of the following characteristics over a period of at least one year upon autoclaving and storage at a temperature above the freezing point of the composition:
- (i) a change in percent encapsulation of no more than about 5%;
 - (ii) a change in phospholipid concentration of no more than about 10% by weight;
 - (iii) a change in concentration of lipophilic amine due to chemical hydrolysis and/or oxidation of no more than about 5% by weight;
 - (iv) a lack of formation of visible aggregates;

- (v) a change in the mass median diameter of no more than about 10% as determined optically.

118. A stable liposome composition of claim 1, when prepared by the method of claim 79.
- 5 119. A sterile and stable liposome composition of claim 41, when prepared by the method of claim 80.
120. A pharmaceutical composition comprising a liposomal composition according to any one of claims 1 through 78.
- 10 121. The use of a liposome composition according to any one of claims 1 through 78, as a medicament.
122. The use of 121, wherein the medicament is administered via inhalation through the pulmonary system, topically, or parenterally.
123. The use according to claim 122, wherein the topical medicament is suitable for ophthalmic administration.
- 15 124. The use according to claim 122, wherein the medicament is suitable for pulmonary administration.
125. A device for containing a stable liposome composition as claimed in claim 1 and being droplets for inhalation of the composition by a patient.
- 20 126. A kit for delivery of a pharmaceutical agent to a patient, the kit comprising instructions for use, a device containing a stable liposome composition as claimed in claim 1 and being capable of generating aerosol droplets of the composition for inhalation by a patient.
127. A method of increasing the stability of liposome compositions, said method comprising the steps of:
- 25 (a) providing a suitable aqueous medium;

- (b) providing a suitable phospholipid;
- (c) providing at least one pharmaceutical agent being capable of being at least partially encapsulated in the liposomes, and being selected from:
- 5 (i) a lipophilic amine and a pharmaceutically acceptable acid, wherein the pharmaceutically acceptable acid is selected from an organic or inorganic acid, and
- (ii) a pharmaceutically acceptable organic acid salt of a lipophilic amine, and optionally a pharmaceutically acceptable organic acid;
- 10 wherein quantity of the pharmaceutically acceptable acid present in the composition is such that the pH of the liposome composition is less than or approximately equal to the pK_a of the amino group of the pharmaceutically active lipophilic amine;
- (d) combining the aqueous medium, phospholipid and pharmaceutical agent to form the liposome composition; and
- 15 (e) autoclaving said liposome composition at conditions effective to sterilize said compositions, thereby affording compositions with increased stability relative to the stability of the composition prior to autoclaving.

128. The method according to claim 127, wherein the step of autoclaving is carried out at a temperature of about 121°C for a minimum of about 15 minutes under an
20 inert atmosphere.

129. The method of claim 128, wherein the inert atmosphere during autoclaving comprises argon or ~~nitrogen~~.

130. A method of identifying a phase stable liposome composition, the method comprising the steps of:

- (a) providing a liposome composition comprising a phospholipid, an aqueous solution, a pharmaceutical agent, and optionally ethanol and a sterol,
- (b) optically determining the mass median diameter ($d(0.5)$) value of the liposome composition;
- 5 (c) centrifuging the liposome composition at between about 1000g and about 5000g, at about 4°C for about 2 hours;
- (d) optically determining the mass median diameter ($d(0.5)$) value of the supernatant portion of the liposome composition solution after centrifugation step (c);
- 10 (e) calculating the ratio of the mass median diameter ($d(0.5)$) particle size distribution value of the solution after centrifugation to that of the solution prior to centrifugation;
- wherein a phase stable liposome composition is identified as such if the composition has a ratio in step (e) of about 0.6 or greater.
- 15 131. A method of claim 130, wherein the phase stable liposome composition is identified as such if the composition has a ratio in step (e) of about 0.8 or greater.
132. A method of claim 130, wherein prior to centrifugation the composition is autoclaved.